# 2 SYNOPSIS

| Name of Sponsor/Company<br>Osmotica Pharmaceutical US LLC | Name of Finished Product<br>Arbaclofen extended-release tablets | Name of Active Ingredient<br>Arbaclofen |
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| Protocol Number: OS440-3004 | | |
| Title of Study: A Randomized, Double-Blind, Placebo-Controlled Parallel Group Study to Investigate the Safety and Efficacy of Arbaclofen Extended-Release Tablets for the Treatment of Spasticity in Patients with Multiple Sclerosis (Study OS440-3004) | | |
| Investigators and Study Centers: 82 Investigators across the United States and Central and Eastern Europe (Russia, Belarus, Serbia, Bosnia and Herzegovina, Croatia, Bulgaria, Moldova, Poland, Ukraine). | | |
| Publication (reference): None | | |
| Study Period (years): < 1 year<br>Date of First Enrollment: 13 February 2018<br>Date of Last Completed: 03 December 2018 | Phase of Development: Phase 3 | |
| Objectives: The primary objective of this study was to demonstrate the safety and efficacy of arbaclofen extended-release tablets (AERT) for treatment of spasticity in patients with multiple sclerosis (MS). | | |
| Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of oral AERT in MS patients with spasticity. Two doses of AERT, 40 mg/day and 80 mg/day, were compared with placebo in a 1:1:1 ratio. Eligible patients underwent up to a 21-day washout period for withdrawal of all medications used for anti-spasticity and/or muscle relaxation prior to randomization. A baseline clinical evaluation was performed (Visit 2) to confirm eligibility for study randomization, and subjects were randomly assigned to one of the 3 treatment arms. Treatment comprised a 9-day titration period; then a 75-day maintenance period at a fixed-dose of either AERT 40 mg, AERT 80 mg, or placebo; and a 7-day taper period, followed by a final safety evaluation. | | |
| Number of Subjects (planned and analyzed): Approximately 510 subjects (170 in each treatment group) were planned to be randomized. The actual number enrolled was 536 subjects at 82 international investigator sites. | | |
| Diagnosis and Main Criteria for Inclusion: In order to be considered eligible, all of the following criteria must have been met:<br>1. Subjects 18 to 65 years of age, inclusive.<br>2. An established diagnosis per McDonald Criteria of MS (either relapsing-remitting or secondary-progressive course) that manifested a documented history of spasticity for at least 6 months prior to Screening.<br>3. Spasticity due to MS as shown by a total numeric-transformed modified Ashworth Scale score of the most affected limb (TNmAS-MAL) score ≥ 2.<br>4. Expanded Disability Status Scale (EDSS) score ≥ 3.0.<br>5. If receiving disease-modifying medications (e.g., interferons approved for MS, glatiramer acetate, natalizumab, fingolimod, or mitoxantrone), there must have been no change in dose for at least 3 months prior to Visit 1 (Screening), and the subject was willing to maintain this treatment dose for the duration of the study. If receiving AMPYRA® (dalfampridine, fampridine, 4-amino puridine), subject must have been at a stable dose for at least 3 months prior to Visit 1 (Screening).<br>6. Stable regimen for at least 3 months prior to Visit 2 (Baseline) for all medications and non-pharmacological therapies that are intended to alleviate spasticity.<br>a. Subjects taking medications indicated for the treatment of spasticity (e.g., baclofen, benzodiazepines, cannabinoids, carisoprodol, dantrolene, tizanidine, cyclobenzaprine, any neuroleptic, ropinoprole, tolperisone, and clonidine) at Visit 1 (Screening) were to wash out from these medications for at most 21 days by Visit 2 (Baseline) in order to be eligible for randomization. Subjects found not to meet this criterion were withdrawn from the study and considered screen failures. | | |

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7. Absence of infections, peripheral vascular disease, painful contractures, advanced arthritis, or other conditions that hindered evaluation of joint movement.
8. Creatinine clearance, as calculated by the glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease Study formula, of > 50 mL/minute.
9. Use of a medically highly effective form of birth control during the study and for 3 months thereafter for women of childbearing potential (including female subjects and female partners of non-sterile male subjects). Use of a medically highly effective form of birth control during the study and for 3 months thereafter for any subject whose partner is not sterilized or post-menopausal.
10. Willing to sign the informed consent form.

Subject Disposition: A total of 594 potential subjects were screened for this study, and 536 were randomized to receive the study medication: 179 subjects each were assigned to receive AERT 40 mg and AERT 80 mg, and 178 were assigned to receive placebo. A total of 403 subjects (75.2%) completed the study; 133 subjects (24.8%) discontinued from the study early, including 42 AERT 40 mg subjects (23.5%), 72 AERT 80 mg subjects (40.2%), and 19 placebo subjects (10.7%). The most common reason for early termination in each group was adverse events (AEs) (90 subjects [16.8%] overall), including 22 (12.3%), 57 (31.8%), and 11 (6.2%) subjects in the AERT 40 mg, AERT 80 mg, and placebo groups, respectively.

Key Demographics: The majority of subjects in the Intent-to-Treat (ITT) population were white (97.4%), were not Hispanic or Latino (95.5%), and were female (59.5%). The mean (SD) age was 46.5 (9.60) years (range, 21 to 65). Height ranged from 142 to 198 cm. The mean (SD) weight was 70.85 (15.182) kg (range, 36.5 to 126.0 kg). The mean (SD) body mass index (BMI) was 24.648 (4.6036) kg/$m^2$ (range, 16.23 to 42.52 kg/$m^2$). Demographic and baseline characteristics were generally balanced across treatment groups.

Test Product, Dose and Mode of Administration, Batch Number: AERT, 40 mg (20 mg twice daily [BID]) and 80 mg (40 mg BID), administered orally without regard to food, batch numbers 170093, 170171, and 170292

Duration of Treatment: A 9-day titration period, a 75-day maintenance period, and a 7-day taper period.

Reference Therapy, Dose and Mode of Administration, Batch Number: matching placebo tablets, batch numbers 16006, 170167, and 170304

Endpoints for Evaluation:
Efficacy:
The co-primary efficacy endpoints were:

- TNmAS-MAL
- Clinical Global Impression of Change (CGIC)

The secondary efficacy endpoints were:

- Expanded Disability Status Scale (EDSS)
- Patient Global Impression of Change (PGIC)
- Total numeric-transformed modified Ashworth Scale score of total limbs (TNmAS-TL)

Safety:
The safety variables evaluated were AEs, vital signs, clinical laboratory test results, 12-lead ECGs, the Urinary Symptom Profile (USP) questionnaire, and the C-SSRS.

Statistical Methods:
Analysis Populations:

- Screened population: Includes all subjects who were considered for this study and provided informed consent, regardless of participation.
- Intent-to-Treat (ITT) population: Includes all subjects who were randomized. The ITT population was used for analyses of accountability, demographics, baseline characteristics, and efficacy.
- Modified ITT (mITT) population: Includes the ITT population minus any subjects with MS relapse. This was a secondary supporting population for the co-primary efficacy analyses.

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- Safety population: Includes all subjects who received at least one dose of double-blind study treatment and had at least one postdose visit. Subjects were analyzed according to the treatment received. This population was used for all safety analyses.
- Per-Protocol (PP) population: Includes all subjects who completed study treatment and had no significant protocol deviations. This was a secondary supporting population for the co-primary efficacy analyses.

Interim Analysis: none

Primary Endpoints:
The AERT 40 mg dose was compared with placebo first (for both TNmAS-MAL and CGIC). If both comparisons were significant at the 0.05 level, then the AERT 80 mg dose was tested at the 0.05 level (both TNmAS-MAL and CGIC). The Day 84 comparison was the primary time point for both co-primary endpoints. For the TNmAS-MAL, the outcome variable was change from baseline score. As the CGIC is a change score with no value measured at baseline, the outcome variable was CGIC score. The TNmAS-MAL and CGIC were analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for treatment, visit, country, and the treatment-by-visit interaction; and, for the TNmAS-MAL, with baseline score as a covariate. Study visit was included in the model as a categorical variable (Visit 4 [Day 42] and Visit 5 [Day 84]) along with the treatment-by-visit interaction. The least-squares mean (LS mean) was used to compare treatments. A number of sensitivity analyses were performed to assess the robustness of the results of the primary analyses and to test the assumptions of the MMRM model.

Secondary Endpoints:
Secondary efficacy endpoints were summarized descriptively and analyzed using the same type of MMRM analyses used for the co-primary efficacy endpoints. The PGIC followed the same MMRM that was used for CGIC. The EDSS and TNmAS-TL followed the same MMRM that was used for TNmAS-MAL.

Safety Analysis:
All safety analyses were conducted using the safety population. Safety assessment was based on descriptive statistics and individual subject listings. No statistical tests were performed for any of the safety assessments.

Summary of Results:
Efficacy:

The co-primary endpoints were the change from baseline to Day 84 in TNmAS-MAL scores and the CGIC scores on Day 84. Statistically significant improvement (decrease) from baseline to Day 84 in TNmAS-MAL scores was noted for each active treatment group (AERT 40 mg, AERT 80 mg, and AERT combined groups; $p < 0.0001$ for each group). There was statistically significantly greater improvement from baseline to Day 84 in TNmAS-MAL scores in the AERT 40 mg group compared to the placebo group, based on the results of MMRM analysis performed with the primary analysis population (the ITT population; $p = 0.0482$). The LS mean CGIC score in the AERT 40 mg group was statistically significantly improved (slightly improved) but was not statistically significantly different from the placebo group at Day 84 ($p = 0.4272$). As such, the study results did not meet the co-primary endpoint.

Conclusions regarding the statistical significance of the AERT 80 mg dose results for the TNmAS-MAL and CGIC endpoints are presented as exploratory. There was statistically significantly greater improvement from baseline to Day 84 in TNmAS-MAL scores in the AERT 80 mg group compared to the placebo group, based on the results of MMRM analysis performed with the primary analysis population (the ITT population; $p = 0.0118$). The CGIC score in the AERT 80 mg group was not statistically significantly different from zero (no change) and was statistically significantly different (lower) from that of the placebo group at Day 84 ($p = 0.0005$).

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There was statistically significantly greater improvement from baseline to Day 42 in TNmAS-MAL scores in the AERT 40 mg group, compared to the placebo group, based on the results of MMRM analysis performed with the primary analysis population (the ITT population; p = 0.0211) and for the 80 mg group compared to the placebo group (p = 0.0022). The results of the sensitivity analyses using the mITT population were consistent with the ITT results.

The TNmAS-MAL scores showed statistically significant greater improvement from baseline to Day 84 in the AERT 40 mg group compared to the placebo group in sensitivity analyses using MMRM analysis performed with the PP population (p = 0.0341) and with treatment-by-country effect included in the model (p = 0.0254). The TNmAS-MAL scores also showed statistically significant greater improvement from baseline in the AERT 40 mg group compared to the placebo group in a sensitivity analysis using MMRM analysis and averaged Day 42 and Day 84 scores (p = 0.0312). For the 80 mg group, these analyses also showed statistically significant greater improvement from baseline to Day 84 (MMRM analysis performed with the PP population [p = 0.0108] and with treatment-by-country effect included in the model [p = 0.0405]; MMRM analysis and averaged Day 42 and Day 84 scores [p = 0.0067]).

No statistically significant differences in the mean CGIC score were observed between the placebo group and the AERT 40 mg group based on the results of MMRM analysis performed with the primary analysis population (the ITT population) or with sensitivity analyses using the mITT population, the PP population, with treatment-by-country interaction effect included in the model, with penalized scores, or with the average of Day 42 and Day 84 scores. In all analyses, the AERT 40 mg mean CGIC score was positive (improvement) and was not statistically significantly different from placebo. The mean CGIC score in the AERT 80 mg group was not statistically significantly different from zero (no change).

No statistically significant differences in the mean change in EDSS score from baseline to the Final Visit were observed between the placebo group and the AERT 40 mg group, AERT 80 mg group, or AERT combined group, based on the results of MMRM analysis.

All groups, including placebo, showed statistically significant improvement (decrease) in TNmAS-TL scores from baseline to Day 42 and Day 84 (p < 0.0001 for each group). The results of MMRM analysis indicated the AERT 40 mg, AERT 80 mg, and AERT combined groups had statistically significant greater improvement in TNmAS-TL scores from baseline to Day 42 compared to the placebo group (p = 0.0128, p = 0.0010, and p = 0.0008, respectively). Statistically significant greater improvement in TNmAS-TL scores from baseline to Day 84 was observed in the AERT combined dose group compared with the placebo group based on MMRM analysis (p = 0.0429).

Safety Results:

No deaths were reported during the study.

The incidence of TESAEs in the AERT 40 mg and AERT 80 mg groups was the same as that in the placebo group (6 subjects [3.4%] in each group).

The incidence of TEAEs was slightly higher in the AERT 40 mg and AERT 80 mg groups (138 subjects [77.1%] and 149 subjects [83.2%], respectively) compared to the placebo group (127 subjects [71.3%]).

The majority of TEAEs in each group were mild or moderate in severity, and the incidence of TEAEs considered severe was low and similar between groups: 9 subjects (5.0%), 10 subjects (5.6%), and 13 subjects (7.3%) in the AERT 40 mg, AERT 80 mg, and placebo group, respectively, experienced severe TEAEs. Severe TESAEs were experienced by 1 subject in each group.

The incidence of potentially treatment-related TEAEs (TEAEs with a relationship considered “possible” or “probable”) was higher in the AERT 40 mg and AERT 80 mg groups (95 subjects [53.1%] and 127 subjects

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[70.9%], respectively) compared to the placebo group (74 subjects [41.6%]). Treatment-emergent SAEs considered potentially treatment-related were experienced by 2 subjects in the AERT 40 mg group and 1 subject each in the AERT 80 mg and placebo groups.

The incidence of subjects with TEAEs leading to discontinuation of study medication was higher in the AERT 40 mg and AERT 80 mg groups (20 subjects [11.2%] and 56 subjects [31.3%]), respectively) compared to the placebo group (9 subjects [5.1%]). Treatment-emergent AEs leading to discontinuation of study medication that were more frequently reported (≥ 5% between-group difference) in the AERT 80 mg group than in the placebo group included muscular weakness, nausea, asthenia, dizziness, vomiting, and gait disturbance. It should be noted that the TEAEs of muscle weakness, gait disturbance, and asthenia probably denote an improvement in lower extremity spasticity for AERT-treated subjects, thus indicating arbaclofen efficacy. MS patients may rely on muscle stiffness when transferring or walking or to maintain posture. Decreased muscle stiffness may have been perceived by subjects as muscle weakness, provoking an initial difficulty with gait and walking. Gait disturbance was a leading cause of discontinuation in this study. Onset occurred soon after titration completion, and the approximate duration of these AEs ranged from 10 to 40 days and was often self limiting. Therefore, the dose needs to be titrated to each patient's needs and condition.

The most prominent observed TEAEs (e.g., dizziness, fatigue, muscle weakness) were as expected for a centrally acting agent. The relative frequency of these TEAEs did not correlate with overall discontinuation rates (i.e., there was a larger difference from placebo in discontinuation rate than TEAE rate). AERT-treated subjects tended to discontinue much earlier in the study (within 30 days) relative to placebo, broadly implicating the rapid titration schedule. The data suggests that the frequency of early-onset AERT-associated discontinuations may be lessened with a more conservative titration schedule (30 days to target dose) thus improving overall tolerability. No clinically relevant differences between treatment groups were observed in the changes in mean laboratory values, vital signs values, ECG parameter values, or USP parameter values between Baseline and postbaseline study visits.

The C-SSRS assessment showed a low incidence of subjects with any suicidal ideation at Screening (4 subjects [0.7%] overall) and postbaseline study visits (1 subject [0.6%] overall at Visit 6 [Final Visit]). There was also a low incidence of subjects with any suicidal behavior at Screening (5 subjects [0.9%] overall) and postbaseline study visits (1 subject [0.6%] overall at Visit 3 and 1 subject [0.6%] overall at Visit 4). Both postbaseline occurrences of suicidal ideation and suicidal behavior were in the AERT 40 mg group.

**Conclusions:** Although this study did not meet the *a priori* statistical criteria for the co primary endpoints, both the 40 mg/day and 80 mg/day doses of arbaclofen significantly reduced spasticity compared to placebo as assessed by the benchmark measure of spasticity, the TNmAS-MAL. The improvement was most pronounced with the 80 mg/day treatment, indicating a dose-response relationship. CGIC improved with 40 mg/day doses of arbaclofen and was the same (no change) with 80 mg/day. Arbaclofen was not better than placebo at either dose as assessed by the CGIC, but no collective worsening of the clinical perception of subjects' condition was observed. The beneficial effects of an 80-mg/day dose in patients suggest that MS patients who successfully titrate to a therapeutic dose of AERT would benefit overall. Qualitatively, the most prominent neuropsychiatric adverse events were similar among the three treatment groups, and there were no clinically significant laboratory or urinary symptom findings. The safety profile of arbaclofen ER 40-mg and 80-mg daily appears to be acceptable when administered twice daily.

Date of the Report:
05 Jun 2020